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TITLE: A Randomized Study of the Effects of Tibolone on Bone Density, Menopausal Symptoms, and Breast Density in High-Risk Women After Prophylactic Oophorectomy

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13. SUPPLEMENTARY NOTES					
14. ABSTRACT The synthetic steroid tibolone has been shown to improve bone mass, mitigate menopausal symptoms and reduce breast density in women with natural menopause. It has not been evaluated in an abrupt menopause model, as occurs in women at high risk of breast cancer because of inherited risk who undergo prophylactic oophorectomy to reduce breast cancer risk. We had planned to conduct a double-blind randomized placebo-control trial to test the hypotheses that Tibolone would accomplish these goals in high-risk premenopausal women undergoing prophylactic oophorectomy, and provide an alternative for them to manage menopause symptoms without increasing breast cancer risk. Unfortunately, despite several modifications to the protocol, a series of outside events ultimately made it impossible for the project to be completed. Many of the modifications required by the DOD required extensive revisions, all of which were in progress until ultimately the final blow: the US FDA determined that the New Drug Application (NDA) submitted for tibolone by Akzo Nobel's human healthcare business, Organon, is "not approvable". This response follows an amendment to the NDA which Organon filed with the FDA in December 2005. This finally makes it unreasonable to attempt to conduct the trial with an agent that has no future in the U.S. Therefore, the project will be withdrawn, and unspent funds returned to the Department of Defense.					
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Introduction

Women with germline *BRCA1* and *BRCA2* mutations face a lifetime risk of breast cancer of 36-87%, as well as high risks of ovarian cancers, approximately 40% and 20%, respectively. Women who test positive for deleterious *BRCA1/2* mutations are advised to undergo frequent cancer screening and to consider prophylactic surgery. In particular, prophylactic bilateral salpingo-oophorectomy is recommended for premenopausal women because of strong data demonstrating not only a reduction in ovarian cancer risk exceeding 90% in the face of ineffective early detection strategies, but also reduction in breast cancer risk of approximately 50%. However, the optimal timing of surgery is debated, since oophorectomy induces premature menopause, with all of the implications of early estrogen deficiency, including an increased risk of osteoporosis and vasomotor symptoms. Hormone replacement therapy has been shown to increase breast cancer risk in the general population, creating a difficult dilemma for young mutation carriers who undergo surgery to improve survival, but often at a significant cost in quality of life. In this project, we propose to evaluate the agent Tibolone, a synthetic steroid with an attractive safety and efficacy profile, for its ability to prevent bone loss, mitigate menopause symptoms, and modulate breast density in high risk women following prophylactic oophorectomy. We had hoped to provide these women with a safe and effective alternative for management of menopause symptoms and consequences after risk-reducing prophylactic surgery. Unfortunately, this will not now be possible and the proposal is withdrawn.

Body

Task 1. Finalize protocol :

- a. After the 2005 submission to the FDA and DOD-ORP, several required protocol modifications were under development among the project investigators. These were substantive changes. The FDA recommended that the primary study endpoint be changed from measurement of change in bone density to relief of menopausal symptoms. The DOD-ORP required that the NIH Consensus Statement on menopause be used to determine acceptable interventions for amelioration of vasomotor symptoms. Unfortunately, the only agents approved in that statement based on randomized trials are estrogen and progesterone. Randomized trials of other agents – specifically SSRI's, neurontin, and clonidine – were disregarded because they were studied in a special subpopulation exclusively – with breast cancer or using SERM risk reducing agents. Certainly this was a challenge for a study in which the protocol population has significantly elevated breast cancer risk. Neither the potential subjects nor their physicians were comfortable with draft recommendations that hormonal medications be used for symptom management. Nonetheless, all modifications were negotiated and the documents nearly ready for submission when our industry collaborators, who were ready to provide additional tibolone, the study agent, asked us to hold until they received the FDA ruling on their tibolone application. They were optimistic about the pending ruling, but felt cautious. Unfortunately, we were notified that the FDA had labeled tibolone “not approvable”. Given this, we decided that we could not proceed with the revised protocol since even were we to demonstrate efficacy of tibolone, it would not be available for women. All coinvestigators ultimately endorsed this decision.
- b. We have not yet formally notified the DAMD that the project cannot be completed but will do so immediately after submission of this report.

Key Research Accomplishments

- With the assistance of the DAMD Human Subjects committees, we developed detailed protocols quantifying and specifying means of studying vasomotor symptoms and their modulation. These protocols can be made available to others interested in studying this difficult question in a surgical population.
- We learned much about the FDA process and found the FDA to be extremely helpful in guiding us through a challenging process.
- We were able to develop and implement systems for identifying and recruiting BRCA1/2 carriers undergoing prophylactic surgery that were extended to other research protocols.
- Unfortunately, we were unable to address the primary question of this proposal.

Reportable Outcomes

Not applicable

Conclusion

To our great disappointment, despite the extensive efforts of our investigative team and the Department of Defense Human Subjects committees, we are unable to conduct this project and address this very troublesome question affecting quality of life for a group of women at exceptional risk of developing breast cancer, who must often choose between comfort and sleep and maximum non-surgical reduction in breast cancer risk.

References

Not applicable

Appendices

Not applicable